Sleep and Sleep Disorders in Patients with Laron Syndrome

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Zvi Laron, Rivka Kauli and Eyal Rosenzweig

Core Message

› Many patients with Laron syndrome complain of sleep disorders. Polysomnographic examination revealed obstructive sleep apnea (OSA) caused by the obesity and narrow oro-pharynx.

35.1 Sleep Quality

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35.1.1 Introduction

The information on sleep disorders including obstructive sleep apnea (OSA) in growth hormone deficiency is scant. Vgontzas et al. (2006) write that "mild GH deficiency has been described in patients having sleep apnea," and Gislason and Almquist (1987) mention that treatment of sleep apnea appears to improve the growth hormone and IGF-I levels. On the other hand, Franco Ramos et al. (2006) reported that GH treatment to obese adults increased the severity of OSA. Sleep apnea has been observed frequently in acromegalic patients mainly over 50 years of age and linked to the macroglossia and craniofacial changes (Grunstein et al. 1991; Hochbau et al. 1999). It was therefore of interest to investigate the sleeping behavior of patients with Laron syndrome (Laron syndrome), a state of hGH inactivity and IGF-I deficiency and severe obesity. We have previously reported severe OSA in a male adult with Laron syndrome (Dagan et al. 2001). Two types of studies were performed.

35.1.2 Method

A prestructured questionnaire (Table 35.1) was constructed and offered for completion during their follow-up visits.

35.1.3 Subjects

Sixteen patients with Laron syndrome – ten females and six adult males and three girls aged 6–12 – completed the whole questionnaire. Eleven patients (six adult females and five adult males) completed the questionnaire on two occasions with at least 3 year intervals; five patients (four females and one male) completed it three times at different ages. All patients were obese.

35.1.4 Results

The summary of 31 questionnaire replies according to score categories is shown in Table 35.2. It is seen that 14 repeated questionnaires to 6 patients scored over 30

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Table 35.1 Questionnaire for the evaluation of sleep quality

Do you have difficulties falling asleep at night
Do you wake up very early in the morning and fail to fall asleep again
Do you take medications for sleep or tranquilizers
Do you fall asleep at daytime (excluding a programmed afternoon nap)
Are you tired in the morning (immediately after waking up)
Do you snore while sleeping (as far as you know) or being told by a relative
Do you wake up from time to time during your sleep
Do you have headaches after waking up from your night sleep
Do you feel tired with no apparent reason
Is your sleep restless with many movements of hands and feet
Do you have complaints of fatigue

Score for each question: 1. never, 2. very rarely, 3. rarely, 4. sometimes, 5. often, 6. very often, 7. always
Sum of scores: 10–24 (good sleep); 25–30 (suspected sleep disturbance – average); >30 (severe sleep disturbance)

Table 35.2 Analysis of responses of the questionnaire for the evaluation of sleep quality

Type of sleep	Number of Laron syndrome patients
Normal	10
Suspected sleep disturbance	7
Severe sleep disturbance	14

denoting a severe sleep disturbance. One of the patients in this category reported that he could not sleep at night and needed to sit up. Of the seven patients with a score of suspected "sleep disturbance," four had normal sleep patterns at their first test taken approximately 3 years before. The patients who reported a normal sleep pattern were the youngest age group. One of the major complaints was fatigue.

35.1.5 Conclusion

Self-reporting using a prestructuring questionnaire is useful in classifying the type of sleep and selecting those subjects who need further investigations. The patients with severe sleep disturbance accepted the advice to undergo polysomnography; those with suspected disturbance remain under observation.

35.2 Severe Obstructive Sleep Apnea (OSA)

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In 2001, we reported severe OSA in a 68-year-old male obese patient with Laron syndrome (MeS) (Dagan et al. 2001). His height was 145 cm; weight, 66 kg; subscapular skinfolds, >40 mm. Since the age of 38, he suffered from Type 2 diabetes mellitus (see Chap. 30) with complications. He received insulin and blood-pressure-lowering drugs. He complained of severe sleepiness, mental fatigue, nervousness, and difficulties in memory, attention span, and concentration. He also noted a dry mouth on waking, and his wife reported that he snored heavily. His sleep was disturbed by sleep-related breathing problems, and so he agreed to undergo two consecutive nights of standard polysomnographic examinations. The tests revealed Time in bed (TIB) = 433 min, Total sleep time (TST) = 355 min, sleep efficiency = 82%, sleep onset latency (SOL) = 8 min, rapid eye movement (REM) = 11.7%, SWS = 10.5%, number of obstructive apneas = 87 (maximum duration = 76.9 s), number of central apneas = 2, number of mixed apneas = 1, number of hypopneas = 345, Apnea Hypopnea Index (AHI) = 58.3, mean overnight SaO_2 = 77.6%, and time snoring = 35.8% (for interpretation see also part III). There were no sleep-related electroencephalogram (EEG) abnormalities, periodic limb movement, and electrocardiogram (ECG) abnormalities (including bradycardia). This information led to the diagnosis of severe obstructive sleep apnea syndrome (OSAS), and he was successfully treated by CPAP (continuous positive air pressure) using a nasal mask during sleep.

35.3 Additional Polysomnographic Examinations of Patients with Laron Syndrome

Eyal Rosenzweig and Zvi Laron

35.3.1 Subjects

Five obese Laron syndrome patients (three men and two women, age range 29–56) who had a score of sleep disturbances of over 30 agreed to undergo

polysomnography at the Institute for Fatigue and Sleep Medicine, Sheba Medical Center (ER).

35.3.2 Method

On admission to the Institute, all subjects underwent standard polysomnography. Recording included EEG, electrooculogram (EOG), electromyogram (EMG); submental and anterior tibialis, ECG, nasal airflow, chest and abdominal breathing movements, snoring, position, and pulse oxymetry. Digital sleep data system (Somnologica 3.2) was used. In the following day, a Multiple Sleep Latency Test (MSLT) was performed according to a standard protocol (Carskadon et al. 1986): five 20-min sleep attempts that took place at 10:00, 12:00, 14:00, 16:00, and 18:00.

35.3.2.1 Sleep Scoring

Polysomnographic data of the nocturnal sleep recordings and MSLT were scored by trained technicians according to the International Classification of Sleep Disorders (American Sleep Disorders Association; Diagnostic Classification Steering Committee 1997).

The following parameters were calculated for the nocturnal sleep report: TST, sleep latency, REM latency, percentage of REM, percentage of SWS, number of arousals (<15 s), number of awakenings (>15 s), sleep efficiency (TST−Time awake/TST), number of apneas, number of hypoapneas, Respiratory Distress Index (RDI; apneas + hypoapneas/hour), number of oxygen desaturations ($<O_2$), and percentage of snoring. MSLT sleep report included SOL and REM latency from sleep onset.

35.3.3 Results

The findings are summarized in Table 35.3 and Fig. 35.1. Five patients completed the sleep evaluation. In one patient, there was no sleep pathology. One patient had moderate OSAS with RDI = 21 and no subjective or objective sleepiness. Sleep stage distribution was normal in this patient. Two patients with normal ESS value have an MSLT of severe objective sleepiness. In these two patients, the most prominent finding on PSG was shortening of SWS. In one of them, REM sleep was also shortened. In these Laron syndrome patients, ESS indicated no objective sleepiness. Another patient with moderate objective sleepiness had a shortened EM sleep with normal SWS. In this patient, ESS value indicated severe subjective sleepiness. Another patient had severe OSAS (RB). The use of CPAP has been recommended to him.

35.3.4 Discussion

Our findings show that not all Laron syndrome patients reporting sleep disturbances have OSAS, despite being very obese (Laron et al. 2006) and having a narrow oropharynx (Kornreich et al. 2002). Until now, we have diagnosed three Laron syndrome patients with severe OSAS;

Table 35.3 Findings at polysomnography in five adult patients with Laron syndrome

Pt.	Age (years)	Sex	S2 (%)	REM (%)	SWS (%)	MSLT	ESS	Snore (%)	$<O_2$ min	ODI	RDI/year	TBF (%)
YR	50	F	45.1	14.6	40.3	10	21	0	90	3.1	2.6	64.5
TS	54	F	70.6	8.3	21.1	2.5	9	70.2	87	0	5.2	58.5
ML	29	M	49.9	16.5	33.6	15.5	1	0.6	–	0	1.1	43.7
BR	42	M	42.2	28.3	29.5	5.1	5	0	–	0	10	44.7
SSh	46	M	44.8	20.4	34.8	15.4	4	4.6	87	1	20.9	36.4

Abbreviations: *F* female; *M* male. Units: *S2* duration of light sleep; *REM* rapid eye movement; *SWS* slow wave sleep; *MSLT* multiple sleep latency; *ESS* Epwarth sleepiness scale; $<O_2$ minimal oxygenation; *ODI* oxygen desaturation index; *RDI* respiratory distress index (apneas + hypopneas/hour); *TBF* total body fat (by DEXA)

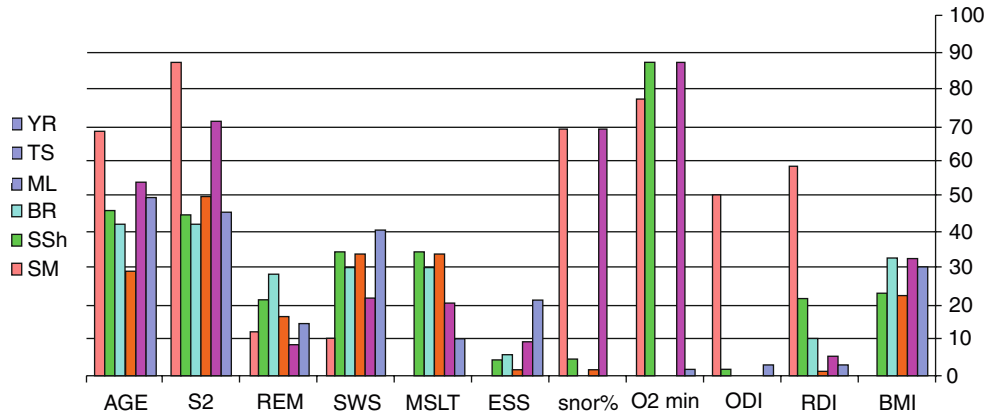

Fig. 35.1 Polysomnography of six patients with Laron syndrome. For explanation of abbreviations see Table 35.3

two of them had Type 2 diabetes mellitus, and both have died (MeS and YG). Whether the OSA has contributed to the development of their vascular complications (Yaggi et al. 2005; Bradley and Floras 2009) is speculative.

35.3.5 Conclusions

As all untreated and even treated patients with Laron syndrome are very obese and tend to have narrowing of the oro-pharynx, sleep disturbances should be looked after and polysomnography performed if indicated. As IGF-I treatment increases the lymphoid tissue, attention should be paid even to the treated young patients.

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